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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/453,801	12/03/1999	Saswati Chatterjee	1954-287	3067

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EXAMINER
LEFFERS JR, GERALD G

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/453,801	CHATTERJEE ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-10,13-15 and 17-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-10,13-15 and 17-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/1/02 as Paper No. 17 has been entered.

In Paper No. 17 several amendments to the claims were made. Several claims were cancelled (claims 6, 11-12 and 16) and several other claims were amended (claims 1-2, 13, 19-21 and 23). Claims 1-5, 7-10, 13-15 and 17-23 are pending in the instant action.

Drawings

Applicants are hereby reminded that a PTO Form 948 with objections to the originally filed drawings was mailed with the first office action (Paper No. 9) on 7/18/01. As indicated on the attachment to the PTO Form 948 mailed with Paper No. 9, applicants are required to submit corrected drawings within the time period set in the attached Office communication (see 37 CFR 1.85(a)). Drawing corrections may no longer be held in abeyance. Failure to submit corrected drawings within the time period set in this action may result in ABANDONMENT of the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-10, 13-15 and 17-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments wherein the hematopoietic cells in the G0 phase of the cell cycle are maintained under conditions where IL-3, IL-6 and cell stimulating factor (CSF) are present, and where cytokine levels are no greater than about 15 ng/ml IL-3, 15 ng/ml IL-6 and 1.5 ng/ml of granulocyte-macrophage colony stimulating factor (GMCSF), does not reasonably provide enablement for embodiments where IL-3, IL-6 and CSF are not present, or where IL-3, IL-6 and GMCSF are at higher than the cited levels. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The nature of the invention is extraordinarily complex, involving the difficult purification of hematopoietic stem cells (e.g. $CD34^{+++}$ $CD38^{-}$ cells) that are in the G0 phase of the cell cycle and maintaining/transducing the cells in such a manner that the cells remain in the G0 phase of the cell cycle, and wherein the transferred DNA remains stably integrated into the genome of the hematopoietic stem cells for at least 4 weeks.

Breadth of the claims: The claimed methods are very specific in that the methods are necessarily performed on hematopoietic stem cells that are in the G0 phase of the cell cycle.

However, the claims are broadly drawn with regard to the cell culture conditions required to maintain the hematopoietic stem cells in the G0 cell-cycle state.

Guidance of the specification: The specification teaches that there are essentially two main critical elements of the claimed methods: 1) purification of the extremely rare hematopoietic stem cells that are in the general cell population and are in the G0 phase of the cell cycle, and 2) maintaining the cells such that the purified hematopoietic stem cells remain in the G0 phase of the cell cycle at least during transduction.

With regard to the first element, the applicants utilized a 3-step approach to isolating a sufficiently large number of purified hematopoietic stem cells in G0 for transduction to have a reasonable chance of success. This 3-step approach involved initial purification of $CD34^+$ cells from mononuclear cells with Multineyi columns, followed by flow sorting of the $CD34^+$ population based upon DNA and RNA content to segregate out only those $CD34^+$ cells which were in the G0 phase, and finally, sorting of the resulting cell population to obtain those cells which were $CD34^+$ and $CD38^-$ (e.g. pages 16-17 of the instant specification; Chatterjee 1.132 Declaration, paragraph 6). The specification teaches that other suitable methods are known in the art for obtaining sufficient numbers of purified hematopoietic stem cells at G0 for transfection (e.g. page 17, line 11 of the instant specification).

With regard to the conditions for maintaining the cells in the G0 state, the specification teaches that under the conditions of the methods of the invention, with particular regard for low cytokine levels, the hematopoietic stem cells in culture remain quiescent for up to 2 days. The specification teaches that in order to perform the method, low levels of the cytokines IL-6, IL-3 and GMCSF are important and that the higher the cytokine levels, the more the cells are

stimulated to undergo mitosis. Alternatively, the cells will die if the levels of the recited factors are too low. For these reasons, the specification teaches that it is advantageous to use cytokine levels of no greater than 15 ng/ml IL-3, 15 ng/ml IL-6, and 1.5 ng/ml of GMCSF (e.g. pages 13-14 of the instant specification). There are no teachings in the instant specification for practicing the claimed methods with culture conditions where IL-3, IL-6 and SCF are not present, or where IL-3, IL-6 and GMCSF are present at levels greater than about 15 ng/ml IL-3, 15 ng/ml IL-6 and 1.5 ng/ml GMCSF.

The existence of working examples: There are no working examples in the instant specification for practicing the claimed methods with culture conditions where IL-3, IL-6 and SCF are not present, or where IL-3, IL-6 and GMCSF are present at levels greater than about 15 ng/ml IL-3, 15 ng/ml IL-6 and 1.5 ng/ml GMCSF.

State of the art: The state of the art with regard to maintaining extremely primitive hematopoietic cells at the G0 phase of the cell cycle at the time of applicants' invention was underdeveloped. In her declaration filed under 1.132 to overcome the prior art (Paper No. 10, filed 1/17/02), Dr. Saswati Chatterjee, one of the instant inventors, states that prior to the instant invention, transduction of extremely primitive, G0, quiescent, pluripotent stem cells had not been demonstrated. Dr. Chatterjee makes clear that the levels of cytokines in the cell culture are critical to maintaining the cells at G0. For instance, Dr. Chatterjee states that the conditions taught by Zhou et al, with relatively high levels of IL-3 and GMCSF, would result in mitosis and loss of the G0 cell cycle status (page 7, paragraph 11). Alternatively, according to Dr. Chatterjee, even if the factors IL-3, IL-6 and GMCSF are present at the levels indicated in the instant specification as being within the optimal range (i.e. IL-3, 10ng/ml; IL-6, 5ng/ml and

GMCSF at 1ng/ml), these factors are not art recognized as being enough to support stem cells. Dr. Chatterjee distinguishes, at least in part, the methods of the instant invention over previous work done by applicants' group, Fisher-Adams et al, based on the observation that cell stimulating factor was present in the methods of the instant specification and was critical for supporting survival of the hematopoietic stem cells (paragraph 9, Paper No. 10).

Predictability of the art: Given the teachings of the instant specification with regard to the difficulties of maintaining the hematopoietic stem cells in the G0 state without inducing mitosis and still maintaining survival, the lack of teachings or working examples in the instant specification or prior art where hematopoietic stems cells are maintained and transduced in culture with culture conditions other than those recited above, practicing the claimed methods with cytokine levels and compositions other than those indicated above would have been unpredictable. One of skill in the are would have had to resort to unpredictable, trial-and-error experimentation in order to develop culturing/transduction conditions where IL-3, IL-6 or SCF were not present, or where cytokine levels are greater than about 15 ng/ml IL-3, 15 ng/ml IL-6 and 1.5 ng/ml of granulocyte-macrophage colony stimulating factor (GMCSF).

The amount of experimentation necessary: Based on the consideration of all of the factors outlined above, it would have required undue, unpredictable experimentation to practice the claimed methods where IL-3, IL-6 or SCF were not present, or where cytokine levels were greater than about 15 ng/ml IL-3, 15 ng/ml IL-6 and 1.5 ng/ml of GMCSF. Therefore, the instant specification is not considered enabling for the full scope of the broadly claimed invention.

Claims 19-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The application discloses adeno-associated virus (AAV) vectors, (vCWRHIVAPAP, vCWRHIVASN, vCWRAP) which are encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

It is unclear whether this biological material is known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. Each of the claims is directed to a specific adeno-associated virus vector, claimed by reference to a specific clone name. As such, the recited name refers to a particular vector having a particular polynucleotide sequence and particular arrangement of critical elements (e.g. specific promoter elements operatively linked in particular spatial arrangement to particular coding sequences).

While the specification provides a general map in Figure 7 demonstrating the general layout of the critical elements of each of the specifically recited vectors, it does not, for example, indicate the approximate distance between elements or that the figure itself is even drawn to scale. The specification provides only general teachings as to how the vectors were constructed based upon a prior art AAV construct, CWRSV. It is not at all clear that the exact sequence of

CWRSV is known in the art or that the base-vector will be available for the full term of any claims that may issue from the instant application. Moreover, the instructions provided in the instant specification for construction of the specific vectors recited in the rejected claims does not allow for the construction of vectors having the exact polynucleotide sequence/arrangement of the recited vectors.

Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
December 6, 2002

DAVID GUZO
PRIMARY EXAMINER

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL ATTACHMENT

A declaration by applicant or assignee, or a statement by applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection or rejection based on a lack of availability of biological material. Such a declaration:

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address. (See 37 C.F.R. § 1.803).

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of the patent. (See 37 C.F.R. § 1.808(a)(2)).

5. States that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. § 1.14 and 35 U.S.C. § 122. (See 37 C.F.R. § 1.808(a)(1)).

6. States that the deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer. See 37 C.F.R. § 1.806).

7. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Alternatively, it may be averred that deposited material has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g., see 961 OG 21, 1977) and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.